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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/735,273	CLARK ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14,17,19,29 and 36-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14,17,19,29 and 36-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 7/15/04 has been entered.

2. This action is written in response to applicant's correspondence submitted 7/15/04. Claims 12, 14, 36, 37, 38, 39, 40, and 41 have been amended. Claims 1-11, 13, 15, 16, 18, 20-28, and 30-35 have been canceled. Claims 12, 14, 17, 19, 29, and 36-41 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Consonant with the previous species election (see paper filed 10/22/02) for claims which recite more than one gene the elected species fibronectin has been examined.

4. The information disclosure statement filed 7/15/04 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The references by An *et al.* were not considered as these references were not provided. Only records from a search database which summarize the references were provided.

These two entries have been lined through for this reason. It has been placed in the application file, but these two references have not been considered.

5. The information disclosure statement filed 7/15/04 further fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the references by Cher and Anderson do not have proper citations as no dates are included. It has been placed in the application file, but these two references have not been considered.

6. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Claim Rejections - 35 USC § 112

7. The rejection of claims 36 and 37 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendments to the claims.

8. The rejection of claims 12, 17, 19, 36, and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of applicant's arguments provided 7-8 of the response and in view of In re Johnson and MPEP 2173.05(i) which specifically states that "If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims."

9. Claims 12, 14, 17, 19, 29, and 36-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The rejection is maintained over the pending claims. The rejection has been modified to clarify the examiner's grounds for rejection.

Nature of the invention

The claims are drawn to methods of predicting the likelihood of development of a metastatic condition via the determination of the level of a gene product which alters the actin-based cytoskeleton of one or more tumor cells, comparison to a control wherein the level relative to the control is determinative of the increased likelihood of developing a metastatic condition. Some claims require only that the biological sample be a "biological sample from a human" and some require that the sample be tumor cells. In some cases the control is a non-metastatic control and a "greater" level of expression is an indicator of increased likelihood, while others recite that the control is a metastatic control and an increased likelihood is indicated if there is equal expression in the sample and the control. Thus, the nature of the invention is within the field of biotechnology, and depends on the knowledge of a correlation between levels of gene products which alter the actin-based cytoskeleton of tumor cells and likelihood of development of metastatic disorder.

Breadth of the claims

Claim 12 is drawn to a method of predicting the likelihood of development of a metastatic condition in a human, comprising the steps of (a) determining the level of one or

more gene products, excluding RhoC, which alter the actin-based cytoskeleton of one or more tumor cells in a human in a biological sample from a human; and (b) comparing the level determined in (a) with a non-metastatic control, wherein if the level determined in (a) is greater than the level of the gene product in the non-metastatic control, then the mammal has an increased likelihood of developing a metastatic condition.

Thus, claim 12 encompasses the detection of the level of any possible gene product that alters the "actin-based cytoskeleton" of any tumor cell. The number of products encompassed within this recitation is enormous and includes hundreds and potentially thousands of products which are both discovered and yet to be discovered. The claim encompasses the use of any biological sample whether or not the sample contains tumor cells. The claim encompasses determining a predisposition to any possible metastatic condition, including those associated with any type of cancer. The claim encompasses the determination of "gene product" which is construed as encompassing assaying for both polypeptide and mRNA. Claim 17 depends from claim 12 and recites a number of possible metastatic conditions, specifically listing metastatic forms of thirteen different cancers and "combinations thereof." Claim 19 depends from claim 12 and recites that the biological sample is a blood sample or a cell sample from a tumor.

Claim 14 differs from claim 12 in that it recites a number of possible gene products, with fibronectin being the species of this listing elected for prosecution. This claim has only been considered in this rejection insofar as it recites fibronectin. Further, claim 14 is limited to determining the level of the gene product in tumor cells. Like claim 12, claim 14 is sufficiently broad so as to include the prediction of an increased likelihood of the development of ANY metastatic condition based on the observance of an increased level of fibronectin gene product,

wherein gene product encompasses at least detecting expressed protein or mRNA. Claim 29 is similar in scope to the elected species of claim 14 but differs in that it only recites that the gene product is fibronectin, while claim 14 recites a Markush group that is limited by election.

Claims 36-41 differ from the preceding claims in that the control is a metastatic control, comparing step (b) states wherein if the level determined in (a) is the same as the level of the gene product in the metastatic control, then the mammal has an increased likelihood of developing a metastatic condition.

As noted, the claims read on predicting the likelihood of development of any possible metastatic condition, with some of the claims being narrowed in that they recite a laundry list of possible conditions, "or combinations thereof." The claims do not recite the nature of the likelihood of development, how this increased or decreased likelihood is to be measured, or what constitutes a clinically or statistically significant change in the likelihood of developing a metastatic condition compared to a control. Some of the claims encompass making predictions based on any tissue sample, and at any point in a human's life. For example, claim 12, as written encompasses the prediction that a healthy patient will develop a metastatic condition at any point in their lifetime, based on, for example, a blood sample.

Further, many of the claims read on determining the level of any gene product or combination of gene products that alter the actin cytoskeleton. The claims do not specifically recite the nature of the alteration of the cytoskeleton, or the manner in which the gene product induces this alteration. Any change in cell shape or size requires an alteration of the cytoskeleton, as does movement of the cell, secretion of products by the cell, endocytosis, pinocytosis, exocytosis, cell division, apoptosis, and many types of transportation of substances

from location to location within the cell. There is an large number of gene products which have the potential to either directly or indirectly affect any of these processes, and thereby alter the cytoskeleton.

Direction and Guidance

The specification teaches the injection of two different melanoma cell lines (one mouse cell line (B16) and one human cell line (A375)) into mice (page 25). From metastatic lesions in these mice, cell lines were developed which were identified as having increased metastatic potential relative to the parental cell lines. Differential display was carried out on these cell lines, and a number of differentially expressed genes were identified (Table 1, p. 19). Three genes, fibronectin, rhoC, and thymosin β4 were identified as being expressed at higher levels in all three metastases selected from both human and mouse samples (p. 30). The specification teaches numerous assays for proliferation, chemotaxis, and metastatic potential of the cell lines (page 28).

Absent from the specification is any guidance as to how the results observed in the differential expression analysis of metastatic melanoma cell lines would be extrapolated to any and all potential types of metastatic conditions. Further, absent from the specification is any guidance as to how one could use a blood sample for the prediction of metastatic potential, as all of the observations in the instant specification are based on tumor cell lines. Absent from the specification is any guidance as to how much difference in "gene product" must be observed in order to conclude that an increased likelihood of development of metastatic condition is present. Further, absent from the specification is any follow-up validation of the differential expression assay, an absence which is critical in view of the unpredictable state of the prior art.

State of the Prior Art / Level of Predictability in the Art

The prior art teaches numerous gene products that alter the actin-based cytoskeleton of one or more tumor that demonstrate an altered level of expression in metastatic tissue. However, it is highly unpredictable within the class of all "actin-based cytoskeleton" altering gene products which would be useful as predictors of metastatic conditions in melanoma or in any other cancer. Suwa, et al., British Journal of Cancer 77(1):147-153, 1998 (hereinafter "Suwa"), for example, teaches a statistically significant correlation between expression of the rhoC gene in pancreatic ductal adenocarcinoma and metastasis. However, Suwa also teaches that no such correlation exists between metastasis and expression of genes closely related to rhoC such as rhoA or rhoB (Suwa, abstract). RhoA and rhoB are also gene products which alter the actin-based cytoskeleton. Indeed, applicant's own specification affirms such a discrepancy for the melanoma cell lines tested herein, teaching at page 9 that RhoA is expressed at equivalent levels in both poorly and highly metastatic tumors.

The prior art demonstrates a high level of unpredictability with regard to the relationship between gene product levels and cancer metastasis. For example, Kawanishi *et al.* (Cancer, April 15, 1999, Vol. 85, No 8, p. 1649) teach that the frequency of lymph node metastases was higher in tumors that were negative for HSP70 gene products in patients with squamous cell carcinoma of the esophagus (p. 1653). On the other hand, Kaur *et al.* (Oral Oncology 34(1998) 496-501) observed that oral cancer patients with elevated levels of HSP70 showed decreased disease free survival rate associated with increased HSP70 gene product, wherein disease free survival includes lack of recurrence or metastasis (p. 499, first column). These papers illustrate that the utilization of gene products as indicators of future prognosis is a highly unpredictable

situation. In a third study, Volm *et al.* (Clin. Exp. Metastasis, 1996, 14, 209-214) were unable to establish any relationship between the expression of HSP70 and the occurrence of metastases in primary ovarian carcinomas.

As another example, Yamamoto *et al.* (Biochemical and Biophysical Research Communications, Vol. 193, No. 2, 1993, p. 706-710) found that the mRNA gene product of the thymosin β-4 gene was present at higher levels in tumors without metastasis than in non-tumorous mucosa, and that this transcript was overexpressed in non0metastatic cells versus metastatic cells. Again, this observation is the opposite of the observation for this same gene in the instant specification. It is highly unpredictable as to which result is more reliable, or why the results differ. For example, do the results differ because the instant examples are concerning melanoma cells and cell lines while Yamamoto *et al.* examined colorectal tumors and cell lines? Do the results differ because the instant examples utilized tumors from a mouse model and Yamamoto *et al.* examined tumors from human tissue? Is there some other reason the results differ, and in fact are opposite of one another? The specification provides no guidance for making this determination, and the consideration of the prior art only highlights the high degree of unpredictability in this invention.

Levedakou *et al.* (Internation Journal of Cancer: 52, 534-537 (1992)) found that Matrix Gla protein was over-expressed in tumor tissues compared to matched normal tissues for renal-cell carcinoma and testicular germ-cell carcinomas. The also found that there for these patients there was an inverse correlation between the level of MGP expression and lymph-node metastasis- that is the LOWER level of MGP was associated with the increased level of metastasis. Again, this observation is opposite that of the instant specification (p. 535). In this

case, Levedakou *et al.* were using DNA probes and Northern analysis to determine expression levels (p. 534).

With regard to claims which recite the measurement of fibronectin (FN) gene product as an indicator of metastatic potential, the prior art repeatedly teaches that the presence or increase of fibronectin expression and/or gene products in tumors is significantly associated with LOW metastatic potential (exactly the opposite result as implied by the instant amended and added claims). For example, Christensen *et al.* (Cancer Research, 48, 6227-6233, 1988) measured FN gene product via staining of the FN protein itself in invasive breast carcinoma and found that while 87% of patients without evidence of metastatic spread had FN positive tumors, only 33% of women with metastatic spread had FN positive tumors (ABSTRACT and throughout). When they tested the metastatic lesions themselves, Christensen *et al.* found that the local recurrences tended to display the same staining pattern, whereas axillary lymph node metastases showed inconsistent staining patterns (p. 6228, paragraph bridging columns). Linlang *et al.* (Journal of Medical Colleges of PLA (1996), 11(3)224-226) teach that decrease or disappearance of FN in basement membrane plays a crucial role in tumor metastasis (p. 226). Xu *et al.* (Baiqiuen Yike Dixue Xuebao (1998) 24(4), 368-369, English abstract provided for applicant's convenience) teach that in the serum of non metastasis patients FN expression was more than double that of the expression in the blood of patients with metastasis lesions, and that the FN expression in the metastasized laryngeal tumor was faint or disappeared. Takei *et al.* (International Journal of Oncology, 12, 517-523, 1998) did not observe an association between FN expression and lymph node metastases or tumor size in invasive breast carcinoma. These references highlight the extreme unpredictability associated with using an increased fibronectin expression observation in

a tumor cell as an indicator of metastatic potential, since it has been shown that decreased FN expression in primary tumor is an indicator of increased metastatic potential, when there was an observable correlation. The instant specification shows only that FN expression is increased in metastatic lesions wherein these lesions originated from melanoma cell lines injected into mice. Cell lines may not be an accurate predictor of actual tumor progression, as these have been thorough multiple passages and crises and have been being kept under artificial conditions. Thus, at best cell lines are a poorer representation of malignancy than the actual tumors examined in the prior art references cited herein because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment.

It is unpredictable whether the discrepancies observed within the prior art and between the data in the prior art and the instant examples are differences in methodology, or differences between different types of cancer, or differences in the activity of gene products at different points in cancer progression, etc. There is no predictable way to determine which possible factor is the most meaningful in attempting to apply the data of the specification or the data in the prior art.

Existence of Working Examples

The specification demonstrates that some genes are differentially expressed in metastatic lesions of cell lines injected into mice, and that in particular fibronectin is over expressed in more highly metastatic cells. With regard to human cancers, only cells which originated from a single human cancer melanoma cell line were examined. The specification does not provide a single working example of the claimed invention, that is an example where

increased gene product was used as an indicator of metastatic potential. The specification does not test blood samples or primary tumor samples, or metastatic lesions that arise from actual primary tumor cells (as opposed to injected cell lines). The specification teaches the use of multiple cell lines of known metastatic potential injected into nude mice (page 25). The specification further teaches the creation of several sublines of A375 cells which over express rhoC, rhoA or GFP (page 28). The specification teaches numerous assays for proliferation, chemotaxis, and metastatic potential of the cell lines (page 28). The specification does not provide working examples of the assay of non-tumor tissue, or even non-metastatic tissue, as having observable differential levels of gene products, all methods which are encompassed within the claimed invention.

Quantity of Experimentation Required

An enormous amount of experimentation would be required in order to practice the claimed invention for the prediction of an increased likelihood of developing melanoma metastases, let alone for the practice of the claimed invention for the prediction of an increased likelihood of predicting any possible metastatic condition in any human, healthy or already presenting with cancer. The experimentation would require the screening of hundreds of potential markers within which alter the actin-based cytoskeleton in any number of possible cancerous conditions in large patient cohorts order to attempt to establish any validated correlation between the presence of gene product at higher levels than non-metastatic tissue and an increased likelihood of developing metastatic conditions. The claims are drawn to the prediction of the likelihood of the development of a metastatic condition in a human based on an increased level of expression of a gene that alter the actin cytoskeleton, some claims particularly

reciting fibronectin as the gene. In order to make and use the invention, one of skill in the art would be required to determine a particular metastatic condition and human for further study. The skilled artisan would then be required to collect biological samples from normal individuals and those suspected of developing a metastatic condition. The level of expression of hundreds of genes would have to be determined, in triplicate to insure accurate results, from all tissue samples. The skilled artisan would then be required to wait, perhaps several years, to evaluate the progression of the metastatic conditions in the tested mammals using some form of objective and quantitative measuring system.

Conclusion

In view of the breadth of the claims, in view of the limited guidance provided by the specification, in view of the unpredictability of the art, in view of the level of experimentation required, the specification does not describe the claimed invention in such a way as to enable one of skill in the art to make and/or use the invention.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 12, 14, 19, 36, 37, 38, and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Kaur *et al.* (Oral Oncology 34 (1998) 496-501).

With regard to claim 12, Kaur *et al.* teach a method comprising the steps of:

(a) determining the level of one gene product which alters the actin-based cytoskeleton of one or more tumor cells in a human in a biological sample from a human, the gene product being HSP70; and (b) comparing the level determined in (a) with a non-metastatic control (p. 497). Kaur *et al.* further teach that the level of HSP70 gene product observed in a biological sample is greater in node positive cancers (metastatic cancers) than when compared to node negative cancers (non-metastatic) (p. 498).

With regard to claim 14, Kaur *et al.* teaches the gene product is HSP70. It is noted that HSP70 is not the elected species, but for this claim no art was located related to the elected species, and so a non-elected species was selected for further consideration.

With regard to claim 19, the sample is a cell sample (tumor cells within tumor tissues).

With regard to claim 36, Kaur *et al.* teach a method comprising the steps of (a) determining the level of one gene product which alters the actin-based cytoskeleton of one or more tumor cells in a human in a biological sample from a human, the gene product being HSP70; and (b) comparing the level determined in (a) with a metastatic control (p. 497). Kaur *et al.* compare the results of the testing of 22 metastatic lesions with one another, and thus meet the limitation of step (b). Kaur *et al.* further teach that the level of HSP70 gene product observed in a the biological sample (tumor tissue from a node positive tissue) is the same as those other metastatic controls in that all of these have "elevated" levels of HSP70 (p. 498).

With regard to claim 37, the sample is a cell sample (tumor cells within tumor tissues).

With regard to claim 38, Kaur *et al.* teaches the gene product is HSP70. It is noted that HSP70 is not the elected species, but this claim is included in the rejection because it does recite HSP70.

With regard to claim 39, the sample is a cell sample (tumor cells within tumor tissues).

Thus, the method taught by Kaur *et al.* appears to meet all of the structural limitations of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 36, 37, 38, 39, 40, 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christensen *et al.* (Cancer Research 1988).

With regard to claims 36 and 40, Christensen *et al.* teach a method comprising the steps of (a) determining the level of one gene product which alters the actin-based cytoskeleton of one or more tumor cells in a human in a biological sample from a human, the gene product being Fibronectin; and (b) comparing the level determined in (a) with a metastatic control (p. 6227).

Christensen *et al.* compare the results of the testing of metastatic lesions with one another, and thus meet the limitation of step (b). Christensen *et al.* further teach that the level of FN gene product observed in a the biological sample (tumor tissue from a node positive tissue) is the same as those other metastatic controls in that all of these have "lower" levels of FN than non-metastatic samples and teach that FN staining reaction is an excellent prognostic factor of metastatic potential (p. 498).

With regard to claim 37, the sample is a cell sample (tumor cells within tumor tissues).

With regard to claim 38, Christensen *et al.* teaches the gene product is fibronectin.

With regard to claims 39 and 40, the sample is a cell sample (tumor cells within tumor tissues).

The teachings of Christensen *et al.* do not anticipate the instant claims because the biological samples used by Christensen *et al.* are taken from autopsies, and thus, there is no need to predict if the human has an increased likelihood of developing a metastatic condition. However, in view of the teachings of Christensen *et al.*, it would have been prima facie obvious to have applied the methodologies taught by Christensen *et al.* to the prediction of an increased likelihood of development of a metastatic condition in a human as Christensen *et al.* specifically teach that FN levels are an excellent prognostic factor for metastatic potential. Therefore, in view of the teachings of Christensen *et al.* the instant claims are prima facie obvious.

Response to Remarks

The remarks are addressed as they are presented in turn beginning on page 6 of the response.

The rejections under 112 2nd paragraph are withdrawn, as are the new matter rejections under 112 1st paragraph.

The 112 1st paragraph lack of enablement rejection is maintained and modified further clarify the examiner's position.

Applicants point out at page 8 of the response that the references cited in the enablement rejection employ immunohistochemical or immunostaining methodology to determine the level of fibronectin expression in various lesion or tumor samples, and suggest that the sensitivity and specificity of the immunostaining methodology are hardly comparable to the array technology employed in the examples of the instant invention. However, this is not persuasive. First, the instant claims encompass the use of any methodology for determining the level of the gene product present in the sample, and the specification particularly recites that one possible methodology for accomplishing this goal is the use of antibodies to bind and detect particular protein gene products (p. 13 of the Specification). Further, this argument is not supported by any evidence on the record which helps to reconcile the clearly discrepant observations (in fact exactly opposite observations) concerning gene product fibronecton observed in the prior art and suggested herein. Arguments of counsel are not found to be persuasive in the absence of a factual showing. MPEP 716.01(c) makes clear that

> "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

As noted in the rejection, any explanation for the wide variety of observations within the prior art and between the art and the findings of the instant application are highly unpredictable. It is not possible to determine if these differences are observed due to sample differences, differences in types of cancers, cell lines versus tumors, etc. There is no guidance present in the specification as to how to tease apart all of these variables and draw predictive conclusions in view of the prior art.

Applicants point out that obtaining biological samples can be performed by well-known methods in the art (arguments p. 9). This is not disputed. The issue with the breadth of the claims with regard to tissue sample is not the physical obtaining of the sample, but instead the question of what conclusions can be drawn from gene product levels in a blood sample relative to future breast or colon cancer metastasis, in a case where a patient already has cancer or does not have cancer, to name a couple of examples. The broadly recited claims encompass this sort of assay, but the specification provides no evidence or guidance as to how to practice such an invention.

Applicant points out that the differential expression of the instant invention was conducted based on samples from pulmonary metastases, not from tumor cell lines. Nonetheless, as discussed in the rejection, it is still highly unpredictable how these findings can be applied in the instant methods due to the fact that they are not validated findings, and the state of the art as a whole coupled with the findings in the instant specification suggest that there is an high degree of unpredictability regarding the presence of gene products of genes which alter the actin based cytoskeleton in general, and fibronectin in particular, and metastatic potential.

Applicants note that the findings that support the instant invention have been published in Nature (bottom of page 9). This is irrelevant when considering the question of lack of enablement. The determination by Nature that the findings were scientifically relevant does not support applicant's claims that the findings are sufficient to establish a reliable predictive relationship for (1) all gene products that alter the actin based cytoskeleton or (2) the elected embodiment of fibronectin in particular.

The premise of applicant's invention is the fact that certain genes were observed to be over expressed in metastatic lesions versus primary tumors in a mouse model using mRNA array analysis. However, applicant has not established that this over expression would be observed anywhere but in a metastatic lesion. That is, applicant has not established that a similar pattern of expression would be observed in a primary tumor that may become metastatic or in the blood of a healthy patient that might develop a metastatic disease or even in the blood of a patient with cancer that may or may not develop a metastatic condition. Thus, for all of the reasons discussed in these arguments, and for all of the reasons set forth in the rejection, the rejection is maintained.

It is not at issue here whether one could perform differential expression assays, it is at issue whether these assays would be predictive in the ways that applicant's claims suggest. Quite simply, the specification has not provide ample evidence to support these claims, in light of the high level of unpredictability in this art, as is highlighted in the case of fibronecitn. The examiner is not requiring knowledge of any exact mechanism of action, but instead evidence of a clear association with predictive value, as is needed to practice the claimed invention.

The rejection discusses a number of factors that have led to the conclusion that undue experimentation would be required to practice the claimed invention, and for this reason, the rejections of record are maintained.

The prior art references in view of van Gronigen *et al.* are withdrawn in favor of rejections which address gene products specifically recited in the instant claims.

The examiner's comments in the advisory action regarding NM23 and laminin were a typographical error and should be disregarded.

Conclusion

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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Juliet C. Switzer
Examiner
Art Unit 1634

September 17, 2004